Hypovitaminosis D and high serum transforming growth factor beta-3: important biomarkers for uterine fibroids risk

Uterine fibroids (UFs, also known as leiomyoma) are the most common benign tumor in the uterus and affect more than 80% of women by age 50. UFs usually cause several symptoms including heavy menstrual bleeding, pelvic pain, subfertility, recurrent pregnancy loss, preterm birth, and other pregnancy-related complications. At present, hysterectomy is the mainstay treatment option for UFs, which leads to a huge economic burden in the Unites States and worldwide. The estimated annual cost for treatment of UFs in the United States is approximately $34 billion (1).

Due to high prevalence, negative health impact, and enormous economic burden, primary preventive strategies as well as novel treatment options for UFs are urgently needed, particularly in younger women who want to preserve their fertility. Although several alternative therapeutic options such as myomectomy, uterine artery embolization, GnRH analogs, and selective P receptor modulators are becoming increasingly available, these methods have some limitations such as serious side effects and high expense, and some might also be incompatible with future pregnancy. Thus, an ideal therapeutic option for prevention and treatment of women with symptomatic UFs should have low risk and cost effectiveness and high efficacy, not preclude future fertility, and be safe for long-term use.

Race also plays an important role in UF risk. African American women have 3–4 times higher incidence of UFs, higher surgery at younger age, multiple larger fibroids, and more severe complications than Caucasian women (2). The etiology of this racial/ethnic disparity is still not fully understood. In 2010, Halder et al. reported at an Society for Gynecologic Investigation (SGI)/Society for Reproductive Investigation (SRI) meeting for the first time that vitamin D deficiency is a novel risk factor for UFs in a cohort of African American and Caucasian women from southern U.S. states (2, 3). Their observation was subsequently confirmed independently in two distinct populations from central Europe and the eastern United States (2). Vitamin D deficiency is present in almost all races; however, it is particularly prevalent in African Americans likely due to their darker skin pigmentation (2). Thus, this important observation can at least provide a partial explanation for the high ethnic disparity of UFs in women of color. Vitamin D plays a role as an antiproliferative and anti-inflammatory agent, and it is present in oily fish, cod liver oil, and many dairy products, while the main source of vitamin D is sun exposure. Serum vitamin D (25-hydroxyvitamin D3) is the major circulating form of vitamin D, and serum levels are an index of vitamin D status in the human body. The normal level of circulating 25-hydroxyvitamin D3 [25(OH) D3] is 30–80 ng/mL (2). Vitamin D deficiency can be defined when serum levels of 25(OH)D3 fall below 20 ng/mL, and insufficiency is defined at levels between 20 and 30 ng/mL. However, 25(OH) D3 is biologically inactive and required to be activated by hydroxylation in the kidney, and likely other organs as well, by the enzyme 1α-hydroxylase, the biologically active 1α, 25-dihydroxyvitamin D3 (1α, 25$(OH)_2$D3), which can bind and signal through its vitamin D receptor (VDR). Vitamin D can modulate gene expression in a tissue-specific manner that can lead to inhibition of cellular proliferation, differentiation, and apoptosis, among a plethora of other cellular effects (2).

Recently, numerous studies have evaluated the effect of vitamin D3 on UF cells and showed that vitamin D3 inhibits cell proliferation through various mechanisms including inhibition of PCNA, cyclin D1, Cdk1, and Bcl2 and suppression of COMT activity in human fibroid cells (2). Elevated expression of estrogen and P receptors (ER-α, PR-A, and PR-B) was also confirmed in human UFs, and treatment with vitamin D3 inhibited those receptors in human UF cells. It has also been established that administration of vitamin D3 or paricalcitol, a potent VDR activator, effectively inhibits human UF cell proliferation in vitro and shrinks fibroid tumor lesions in well-established preclinical animal models (2). Thus, based on available published literature, it is evident that vitamin D and other VDR agonists might be potent antitumor/anti-inflammatory agents that can be considered as nonsurgical orally administered therapeutic options for the effective, safe, and long-term medical treatment and/or prevention of UFs. However, well-designed human therapeutic and preventative clinical trials are yet to confirm the utility of vitamin D in patients with symptomatic UFs.

The transforming growth factor beta (TGFβ) is known as a multifunctional cytokine that has three isoforms, 1, 2, and 3. TGFβs play a key role in the regulation of cell growth and proliferation and differentiation, as well as tissue remodeling. These processes can play a role in the development of tissue fibrosis. UFs are characterized by excessive production and deposition of extracellular matrix (ECM). It has been well-established that the level of TGFβ3 is elevated 3–5 times in human UFs as com-pared with adjacent normal myometrium (2). Moreover, elevated levels of TGFβRII were also observed in UFs as compared with adjacent normal myometrium. The TGFβ3 isoform plays a pivotal role in the synthesis of many of the ECM proteins that are associated with tissue fibrosis. TGFβ3 stimulates the synthesis of collagen type 1 and fibronectin as well as ECM-associated proteoglycans, while treatment with vitamin D3 reduces ECM-associated collagen type 1, fibronectin, and plasminogen activator inhibitor-1, which are well-known TGFβ-regulated genes. Studies have also suggested that administration of vitamin D3 potentially reduced TGFβ3-induced Smad activation as well as reduction of TGFβ3-dependent key profibrotic factors in human UF cells (4). Interestingly, in their manuscript in this issue of *Fertility and Sterility*, Ciebiera et al. demonstrate that higher body mass index (BMI), family history, lower serum vitamin D, and higher concentrations of serum TGFβ3 are significant risk factors for UFs in an independent cohort from Poland (5). The manuscript is impactful since the authors included detailed epidemiological data to establish the risks of development of human UFs and emphasize the role of vitamin D

deficiency and increased TGFβ3 serum concentrations as established risk factors and viable biomarkers for UFs. In that article, the authors presented data from a total of 188 Caucasian subjects, of whom 105 were fibroid subjects and 83 were normal subjects with no pathological evidence of UFs (5). The significant association between lower serum levels of vitamin D and UF occurrence in an independent unique cohort from Eastern Europe suggests that such an association is a global phenomenon. Additionally, the higher serum concentration of TGFβ3 is interesting as it is consistent with the well-established local effects of TGFβ3 in UF tissues. Previous studies have established elevated levels of TGFβ3 mRNA in UFs compared with adjacent normal myometrium, and in this manuscript, the authors report that increased serum concentrations of TGFβ3 in UF patients suggest that this cytokine affects fibroid development in an autocrine, paracrine, and endocrine manner. However, a direct causality between vitamin D deficiency and increased serum concentrations of TGFβ3 is not yet established. As the authors mentioned, TGFβ3 is a nonspecific marker, and thus it is imperative to establish the serum concentration of TGFβ3 in a larger population to establish this statement. These novel biomarkers for UF risk conceivably revive the concept of UF prevention in a high-risk population. Combining these easily measurable serum biomarkers with other anthropometric measures (high BMI), strong family history, and racial tendencies (African ancestry) constitutes a reliable screening tool to identify women at higher risk for future development of symptomatic UFs. In turn these presymptomatic women can potentially be offered preventative measures such as regular imaging evaluation and correction of vitamin D deficiency among others (2). While novel therapeutic products are being developed for oral and localized UF treatment that will no doubt provide useful tools against this major clinical challenge, we believe that such a highly prevalent disease with clear easily detected risk factors is a ripe candidate for an ambitious cost-effective prevention strategy.

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REFERENCES

1. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BK, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 2012;206:211.e1–9.
2. Brakta S, Diamond JS, Al-Hendy A, Diamond MP, Halder SK. Role of Vitamin D in uterine fibroid biology. Fertil Steril 2015;104:698–706.
3. Halder SK, Sharan C, Harirah H, Al-Hendy A. Lower serum levels of vitamin D3 is a risk factor for uterine fibroids in African Americans. Abstracts of the 57th Annual Scientific Meeting of the Society for Gynecologic Investigation, March 24–27, 2010, Orlando, Florida, USA. Reprod Sci 2010;17(3 Suppl):273A–4A.
4. Al-Hendy A, Badr M. Can vitamin D reduce the risk of uterine fibroids? Womens Health (Lond) 2014;10:353–8.
5. Ciebiera M, Włodarczyk M, Słabuszewska-Jóźwiak A, Nowicka G, Jakiel G. The influence of vitamin D and transforming growth factor beta 3 serum concentrations, obesity, and family history on the risk for uterine fibroids. Fertil Steril 2016;106:1787–92.